ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ALIMTA 500 mg powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 500 mg of pemetrexed (as pemetrexed disodium).

Each vial must be reconstituted with 20 ml of sodium chloride 9 mg/ml (0.9 %) solution for injection resulting in 25 mg/ml of solution. The appropriate volume of required dose is removed from the vial and further diluted to 100 ml with sodium chloride 9 mg/ml (0.9 %) solution for injection (see section 6.6.).

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

A white to either light yellow or green-yellow lyophilised powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ALIMTA in combination with cisplatin is indicated for the treatment of chemotherapy naïve patients with unresectable malignant pleural mesothelioma.

ALIMTA is indicated as monotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy.

4.2 Posology and method of administration

ALIMTA must only be administered under the supervision of a physician qualified in the use of anti-cancer chemotherapy.

The ALIMTA solution must be prepared according to the instructions provided in section 6.6.

Malignant pleural mesothelioma:
In patients treated for malignant pleural mesothelioma, the recommended dose of ALIMTA is 500 mg/m^2 of body surface area (BSA) administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle. The recommended dose of cisplatin is 75 mg/m^2 BSA infused over two hours approximately 30 minutes after completion of the pemetrexed infusion on the first day of each 21-day cycle. Patients must receive adequate anti-emetic treatment and appropriate hydration prior to and/or after receiving cisplatin (See also cisplatin Summary of Product Characteristics for specific dosing advice).

Non-small cell lung cancer:
In patients treated for non-small cell lung cancer, the recommended dose of ALIMTA is 500 mg/m^2 BSA administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle.

Premedication regimen:
To reduce the incidence and severity of skin reactions, a corticosteroid should be given the day prior to, on the day of, and the day after pemetrexed administration. The corticosteroid should be equivalent to 4 mg of dexamethasone administered orally twice a day (see section 4.4).

To reduce toxicity, patients treated with pemetrexed must also receive vitamin supplementation (see section 4.4). Patients must take oral folic acid or a multivitamin containing folic acid (350 to 1000 micrograms) on a daily basis. At least five doses of folic acid must be taken during the seven days preceding the first dose of pemetrexed, and dosing must continue during the full course of therapy and for 21 days after the last dose of pemetrexed. Patients must also receive an intramuscular injection of vitamin B_{12} (1000 micrograms) in the week preceding the first dose of pemetrexed and once every three cycles thereafter. Subsequent vitamin B_{12} injections may be given on the same day as pemetrexed.

Monitoring:
Patients receiving pemetrexed should be monitored before each dose with a complete blood count, including a differential white cell count (WCC) and platelet count. Prior to each chemotherapy administration blood chemistry tests should be collected to evaluate renal and hepatic function. Before the start of any cycle of chemotherapy, patients are required to have the following: Absolute Neutrophil Count (ANC) should be ≥ 1500 cells/mm^3 and platelets should be ≥ 100,000 cells/mm^3. Creatinine clearance should be ≥ 45 ml/min.
The total bilirubin should be ≤ 1.5 times upper limit of normal. Alkaline phosphatase (AP), aspartate transaminase (AST or SGOT) and alanine transaminase (ALT or SGPT) should be ≤ 3 times upper limit of normal. Alkaline phosphatase, AST and ALT ≤ 5 times upper limit of normal is acceptable if liver has tumour involvement.

Dose Adjustments:
Dose adjustments at the start of a subsequent cycle should be based on nadir haematologic counts or maximum non-haematologic toxicity from the preceding cycle of therapy. Treatment may be delayed to allow sufficient time for recovery. Upon recovery patients should be retreated using the guidelines in Tables 1, 2 and 3, which are applicable for ALIMTA used as a single agent or in combination with cisplatin.

Table 1 - Dose Modification Table for ALIMTA (as single agent or in combination) AND Cisplatin –Haematologic Toxicities	
Nadir ANC < 500 /mm^3 and nadir platelets ≥ 50,000 /mm^3	75 % of previous dose (both ALIMTA and cisplatin).
Nadir platelets ≤ 50,000 /mm^3 regardless of nadir ANC	50 % of previous dose (both ALIMTA and cisplatin).

If patients develop non-haematologic toxicities ≥ Grade 3 (excluding neurotoxicity), ALIMTA should be withheld until resolution to less than or equal to the patient's pre-therapy value. Treatment should be resumed according to the guidelines in Table 2.

Table 2 - Dose Modification Table for ALIMTA (as single agent or in combination) and Cisplatin– Non-haematologic Toxicities [a, b]		
	Dose of ALIMTA (mg/m^2)	**Dose for cisplatin (mg/m^2)**
Any Grade 3 or 4 toxicities except mucositis	75 % of previous dose	75 % of previous dose
Any diarrhoea requiring hospitalisation (irrespective of grade) or grade 3 or 4 diarrhoea.	75 % of previous dose	75 % of previous dose
Grade 3 or 4 mucositis	50 % of previous dose	100 % of previous dose

[a] National Cancer Institute Common Toxicity Criteria (CTC)
[b] Excluding neurotoxicity

In the event of neurotoxicity, the recommended dose adjustment for ALIMTA and cisplatin is documented in Table 3. Patients should discontinue therapy if Grade 3 or 4 neurotoxicity is observed.

Table 3 - Dose Modification for ALIMTA (as single agent or in combination) and Cisplatin – Neurotoxicity		
CTC* Grade	**Dose of ALIMTA (mg/m^2)**	**Dose for cisplatin (mg/m^2)**
0 – 1	100 % of previous dose	100 % of previous dose
2	100 % of previous dose	50 % of previous dose

* Common Toxicity Criteria (CTC)

Treatment with ALIMTA should be discontinued if a patient experiences any haematologic or non-haematologic Grade 3 or 4 toxicity after 2 doses reductions or immediately if Grade 3 or 4 neurotoxicity is observed.

Elderly: In clinical studies, there has been no indication that patients 65 years of age or older are at increased risk of adverse events compared to patients younger than 65 years old. No dose reductions other than those recommended for all patients are necessary.

Children and adolescents: ALIMTA is not recommended for use in patients under 18 years of age, as safety and efficacy have not been established in this group of patients.

Patients with Renal Impairment (Standard Cockcroft and Gault formula or Glomerular Filtration Rate measured Tc99m-DPTA serum clearance method): pemetrexed is primarily eliminated unchanged by renal excretion. In clinical studies, patients with creatinine clearance of ≥ 45 ml/min required no dose adjustments other than those recommended for all patients. There are insufficient data on the use of pemetrexed in patients with creatinine clearance below 45 ml/min; therefore the use of pemetrexed is not recommended (see section 4.4).

Patients with Hepatic Impairment: No relationships between AST (SGOT), ALT (SGPT), or total bilirubin and pemetrexed pharmacokinetics were identified. However patients with hepatic impairment such as bilirubin > 1.5 times the upper limit of normal and/or transaminase > 3.0 times the upper limit of normal (hepatic metastases absent) or > 5.0 times the upper limit of normal (hepatic metastases present) have not been specifically studied.

4.3 Contraindications

Hypersensitivity to pemetrexed or to any of the excipients.

Breast-feeding must be discontinued during pemetrexed therapy (see section 4.6).

Concomitant yellow fever vaccine (see section 4.5).

4.4 Special warnings and special precautions for use

Pemetrexed can suppress bone marrow function as manifested by neutropenia, thrombocytopenia and anaemia (see section 4.8). Myelosuppression is usually the dose-limiting toxicity. Patients should be monitored for myelosuppression during therapy and pemetrexed should not be given to patients until absolute neutrophil count (ANC) returns to ≥ 1500 cells/mm^3 and platelet count returns to ≥ 100,000 cells/mm^3. Dose reductions for subsequent cycles are based on nadir ANC, platelet count and maximum non-haematologic toxicity seen from the previous cycle (see section 4.2).

In the Phase 3 mesothelioma trial, overall less toxicity and reduction in Grade 3/4 haematologic and non-haematologic toxicities such as neutropenia, febrile neutropenia and infection with Grade 3/4 neutropenia were reported when pre-treatment with folic acid and vitamin B_{12} was administered. Therefore patients treated with pemetrexed must be instructed to take folic acid and vitamin B_{12} as a prophylactic measure to reduce treatment-related toxicity (see section 4.2).

Skin reactions have been reported in patients not pre-treated with a corticosteroid. Pre-treatment with dexamethasone (or equivalent) can reduce the incidence and severity of skin reactions (see section 4.2).

An insufficient number of patients has been studied with creatinine clearance of below 45 ml/min. Therefore, the use of pemetrexed in patients with creatinine clearance of < 45 ml/min is not recommended (see section 4.2).

Patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 ml/min) should avoid taking non-steroidal anti-inflammatory drugs (NSAIDs) as ibuprofen, and aspirin (> 1.3 g daily) for 2 days before, on the day of, and 2 days following pemetrexed administration (see section 4.5). All patients eligible for pemetrexed therapy should avoid taking NSAIDs with long elimination half-lives for at least 5 days prior to, on the day, and at least 2 days following pemetrexed administration (see section 4.5).

The effect of third space fluid, such as pleural effusion or ascites, on pemetrexed is unknown. In patients with clinically significant third space fluid, consideration should be given to draining the effusion prior to pemetrexed administration.

Due to the gastrointestinal toxicity of pemetrexed given in combination with cisplatin, severe dehydration has been observed. Therefore, patients should receive adequate antiemetic treatment and appropriate hydration prior to and/or after receiving treatment.

Serious cardiovascular events, including myocardial infarction and cerebrovascular events have been uncommonly reported during clinical studies with pemetrexed, usually when given in combination with another cytotoxic agent. Most of the patients in whom these events have been observed had pre-existing cardiovascular risk factors (see section 4.8).

Immunodepressed status is common in cancer patients. As a result, concomitant use of live attenuated vaccines (except yellow fever) is not recommended (see section 4.5).

Pemetrexed can have genetically damaging effects. Sexually mature males are advised not to father a child during the treatment and up to 6 months thereafter. Contraceptive measures or abstinence are recommended. Owing to the possibility of pemetrexed treatment causing irreversible infertility, men are advised to seek counselling on sperm storage before starting treatment.

Women of childbearing potential must use effective contraception during treatment with pemetrexed (see section 4.6).

4.5 Interaction with other medicinal products and other forms of interaction

Pemetrexed is mainly eliminated unchanged renally by tubular secretion and to a lesser extent by glomerular filtration. Concomitant administration of nephrotoxic drugs (e.g. aminoglycoside, loop diuretics, platinum compounds, cyclosporin) could potentially result in delayed clearance of pemetrexed. This combination should be used with caution. If necessary, creatinine clearance should be closely monitored.

Concomitant administration of substances that are also tubularly secreted (e.g. probenecid, penicillin) could potentially result in delayed clearance of pemetrexed. Caution should be made when these drugs are combined with pemetrexed. If necessary, creatinine clearance should be closely monitored.

In patients with normal renal function (creatinine clearance $\geq$ 80 ml/min), high doses of non-steroidal anti-inflammatory drugs (NSAIDs, such as ibuprofen > 1600 mg/day) and aspirin at higher dosage ($\geq$ 1.3 g daily) may decrease pemetrexed elimination and, consequently, increase the occurrence of pemetrexed adverse events. Therefore, caution should be made when administering higher doses of NSAIDs or aspirin at higher dosage, concurrently with pemetrexed to patients with normal function (creatinine clearance $\geq$ 80 ml/min).
In patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 ml/min), the concomitant administration of pemetrexed with NSAIDs (e.g. ibuprofen) or aspirin at higher dosage should be avoided for 2 days before, on the day of, and 2 days following pemetrexed administration (see section 4.4).
In the absence of data regarding potential interaction with NSAIDs having longer half-lives as piroxicam or rofecoxib, the concomitant administration with pemetrexed should be avoided for at least 5 days prior to, on the day, and at least 2 days following pemetrexed administration (see section 4.4).

Pemetrexed undergoes limited hepatic metabolism. Results from *in vitro* studies with human liver microsomes indicated that pemetrexed would not be predicted to cause clinically significant inhibition of the metabolic clearance of drugs metabolised by CYP3A, CYP2D6, CYP2C9, and CYP1A2.

Interactions common to all cytotoxics:
Due to the increased thrombotic risk in patients with cancer, the use of anticoagulation treatment is frequent. The high intra-individual variability of the coagulation status during diseases and the possibility of interaction between oral anticoagulants and anticancer chemotherapy require increased frequency of INR (International Normalised Ratio) monitoring, if it is decided to treat the patient with oral anticoagulants.
Concomitant use contraindicated: Yellow fever vaccine: risk of fatal generalised vaccinale disease (see section 4.3).
Concomitant use not recommended: Live attenuated vaccines (except yellow fever): risk of systemic, possibly fatal, disease. The risk is increased in subjects who are already immunosuppressed by their underlying disease. Use an inactivated vaccine where it exists (poliomyelitis) (see section 4.4).

4.6 Pregnancy and lactation

There are no data from the use of pemetrexed in pregnant women but pemetrexed, like other anti-metabolites, is suspected to cause serious birth defects when administered during pregnancy. Animal studies have shown reproductive toxicity (see section 5.3). Pemetrexed should not be used during pregnancy unless clearly necessary, after a careful consideration of the needs of the mother and the risk for the foetus (see section 4.4).

Women of childbearing potential must use effective contraception during treatment with pemetrexed Pemetrexed can have genetically damaging effects. Sexually mature males are advised not to father a child during the treatment and up to 6 months thereafter. Contraceptive measures or abstinence are recommended. Owing to the possibility of pemetrexed treatment causing irreversible infertility, men are advised to seek counselling on sperm storage before starting treatment.

It is not known whether pemetrexed is excreted in human milk and adverse effects on the suckling child cannot be excluded. Breast-feeding must be discontinued during pemetrexed therapy (see section 4.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, it has been reported that pemetrexed may cause fatigue. Therefore patients should be cautioned against driving or operating machines if this event occurs.

4.8 Undesirable effects

The table below provides the frequency and severity of undesirable effects that have been reported in > 5 % of 168 patients with mesothelioma who were randomised to receive cisplatin and pemetrexed and 163 patients with mesothelioma randomised to receive single agent cisplatin. In both treatment arms, these chemonaive patients were fully supplemented with folic acid and vitamin B_{12}.

System Organ Class	**Frequency**	**Event***	**Pemetrexed/cisplatin (N = 168)**		**Cisplatin (N = 163)**	
			All Grades Toxicity (%)	**Grade 3 - 4 Toxicity (%)**	**All Grades Toxicity (%)**	**Grade 3 - 4 Toxicity (%)**
Blood and Lymphatic System Disorders	Very Common	Neutrophils/ Granulocytes decreased	56.0	23.2	13.5	3.1
		Leukocytes decreased	53.0	14.9	16.6	0.6
		Haemoglobin decreased	26.2	4.2	10.4	0.0
		Platelets decreased	23.2	5.4	8.6	0.0
Eye Disorders	Common	Conjunctivitis	5.4	0.0	0.6	0.0
Gastrointestinal Disorders	Very Common	Nausea	82.1	11.9	76.7	5.5
		Vomiting	56.5	10.7	49.7	4.3
		Stomatitis/ Pharyngitis	23.2	3.0	6.1	0.0
		Anorexia	20.2	1.2	14.1	0.6
		Diarrhoea	16.7	3.6	8.0	0.0
		Constipation	11.9	0.6	7.4	0.6
	Common	Dyspepsia	5.4	0.6	0.6	0.0
General Disorders	Very Common	Fatigue	47.6	10.1	42.3	9.2
Metabolism and Nutrition Disorders	Common	Dehydration	6.5	4.2	0.6	0.6
Nervous System Disorders	Very Common	Neuropathy-Sensory	10.1	0.0	9.8	0.6
	Common	Dysgeusia	7.7	0.0	6.1	0.0

Renal and urinary Disorders	Very Common	Creatinine elevation	10.7	0.6	9.8	1.2
		Creatinine clearance decreased**	16.1	0.6	17.8	1.8
Skin and Subcutaneous Tissue Disorders	Very Common	Rash	16.1	0.6	4.9	0.0
		Alopecia	11.3	0.0	5.5	0.0

* Refer to National Cancer Institute CTC version 2 for each grade of toxicity except the term "creatinine clearance decreased"** which is derived from the term "renal/genitourinary other".

Very common - ≥ 10 %; Common is normally defined as > 1 % and < 10 %. For the purpose of this table a cut off of 5 % was used for inclusion of all events where the reporter considered a possible relationship to pemetrexed and cisplatin.

Clinically relevant CTC toxicities that were reported in > 1 % and ≤ 5 % (common) of the patients that were randomly assigned to receive cisplatin and pemetrexed include: increased AST, ALT, and GGT, infection, pyrexia, febrile neutropenia, renal failure, chest pain, and urticaria.
Clinically relevant CTC toxicities that were reported in ≤ 1 % of the patients that were randomly assigned to receive cisplatin and pemetrexed include arrhythmia and motor neuropathy.

The table below provides the frequency and severity of undesirable effects that have been reported in > 5 % of 265 patients randomly assigned to receive single agent pemetrexed with folic acid and vitamin B_{12} supplementation and 276 patients randomly assigned to receive single agent docetaxel. All patients were diagnosed with locally advanced or metastatic non-small cell lung cancer and received prior chemotherapy.

System Organ Class	**Frequency**	**Event***	**Pemetrexed N = 265**		**Docetaxel N = 276**	
			All Grades Toxicity (%)	**Grade 3 – 4 Toxicity (%)**	**All Grades Toxicity (%)**	**Grade 3 – 4 Toxicity (%)**
Blood and Lymphatic System Disorders	Very Common	Haemoglobin decreased	19.2	4.2	22.1	4.3
		Leukocytes decreased	12.1	4.2	34.1	27.2
		Neutrophils/ Granulocytes decreased	10.9	5.3	45.3	40.2
	Common	Platelets decreased	8.3	1.9	1.1	0.4
Gastrointestinal Disorders	Very Common	Nausea	30.9	2.6	16.7	1.8
		Anorexia	21.9	1.9	23.9	2.5
		Vomiting	16.2	1.5	12.0	1.1
		Stomatitis/ Pharyngitis	14.7	1.1	17.4	1.1
		Diarrhoea	12.8	0.4	24.3	2.5
	Common	Constipation	5.7	0.0	4.0	0.0
General Disorders	Very Common	Fatigue	34.0	5.3	35.9	5.4
	Common	Fever	8.3	0.0	7.6	0.0
Hepatobilliary Disorders	Common	SGPT (ALT) elevation	7.9	1.9	1.4	0.0

		SGOT (AST) elevation	6.8	1.1	0.7	0.0
Skin and Sub-cutaneous tissue disorders	Very Common	Rash/ desquamation	14.0	0.0	6.2	0.0
	Common	Pruritus	6.8	0.4	1.8	0.0
		Alopecia	6.4	0.4	37.7	2.2

*Refer to National Cancer Institute CTC version 2 for each grade of toxicity.

Very common - ≥ 10 %; Common is normally defined as > 1 % and < 10 %. For the purpose of this table a cut off of 5 % was used for inclusion of all events where the reporter considered a possible relationship to pemetrexed.

Clinically relevant CTC toxicities that were reported in > 1 % and ≤ 5 % (common) of the patients that were randomly assigned to pemetrexed include: sensory neuropathy, motor neuropathy, abdominal pain, increased creatinine, febrile neutropenia, infection without neutropenia, allergic reaction/hypersensitivity and erythema multiforme.
Clinically relevant CTC toxicities that were reported in ≤ 1 % of the patients that were randomly assigned to pemetrexed include supraventricular arrhythmias.

Clinically relevant Grade 3 and Grade 4 laboratory toxicities were similar between integrated Phase 2 results from three single agent pemetrexed studies (n = 164) and the Phase 3 single agent pemetrexed study described above, with the exception of neutropenia (12.8 % versus 5.3 %, respectively) and alanine transaminase elevation (15.2 % versus 1.9 %, respectively). These differences were likely due to differences in the patient population, since the Phase 2 studies included both chemonaive and heavily pre-treated breast cancer patients with pre-existing liver metastases and/or abnormal baseline liver function tests.

Serious cardiovascular and cerebrovascular events, including myocardial infarction, angina pectoris, cerebrovascular accident and transient ischaemic attack have been uncommonly reported during clinical studies with pemetrexed, usually when given in combination with another cytotoxic agent. Most of the patients in whom these events have been observed had pre-existing cardiovascular risk factors.

Rare cases of hepatitis, potentially serious, have been reported during clinical studies with pemetrexed.

4.9 Overdose

Reported symptoms of overdose include neutropenia, anaemia, thrombocytopenia, mucositis, and rash. Anticipated complications of overdose include bone marrow suppression as manifested by neutropenia, thrombocytopenia and anaemia. In addition, infection with or without fever, diarrhoea, and/or mucositis may be seen. In the event of suspected overdose, patients should be monitored with blood counts and should receive supportive therapy as necessary. The use of calcium folinate / folinic acid in the management of pemetrexed overdose should be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Folic acid analogues, ATC code: L01BA04

ALIMTA (pemetrexed) is a multi-targeted anti-cancer antifolate agent that exerts its action by disrupting crucial folate-dependent metabolic processes essential for cell replication.

In vitro studies have shown that pemetrexed behaves as a multitargeted antifolate by inhibiting thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT), which are key folate-dependent enzymes for the *de novo* biosynthesis of

thymidine and purine nucleotides. Pemetrexed is transported into cells by both the reduced folate carrier and membrane folate binding protein transport systems. Once in the cell, pemetrexed is rapidly and efficiently converted to polyglutamate forms by the enzyme folylpolyglutamate synthetase. The polyglutamate forms are retained in cells and are even more potent inhibitors of TS and GARFT. Polyglutamation is a time- and concentration-dependent process that occurs in tumour cells and, to a lesser extent, in normal tissues. Polyglutamated metabolites have an increased intracellular half-life resulting in prolonged drug action in malignant cells.

Clinical Efficacy:

EMPHACIS, a multicentre, randomised, single-blind phase 3 study of ALIMTA plus cisplatin versus cisplatin in chemonaive patients with malignant pleural mesothelioma, has shown that patients treated with ALIMTA and cisplatin had a clinically meaningful 2.8-month median survival advantage over patients receiving cisplatin alone.

During the study, low-dose folic acid and vitamin B_{12} supplementation was introduced to patients' therapy to reduce toxicity. The primary analysis of this study was performed on the population of all patients randomly assigned to a treatment arm who received study drug (randomised and treated). A subgroup analysis was performed on patients who received folic acid and vitamin B_{12} supplementation during the entire course of study therapy (fully supplemented). The results of these analyses of efficacy are summarised in the table below:

Efficacy of ALIMTA plus Cisplatin vs. Cisplatin in Malignant Pleural Mesothelioma

	Randomized and Treated Patients		**Fully Supplemented Patients**	
Efficacy Parameter	ALIMTA/ cisplatin (N = 226)	Cisplatin (N = 222)	ALIMTA/ cisplatin (N = 168)	Cisplatin (N = 163)
Median Overall Survival (months) (95 % CI)	12.1 (10.0 - 14.4)	9.3 (7.8 - 10.7)	13.3 (11.4 - 14.9)	10.0 (8.4 - 11.9)
Log Rank p-value*	0.020		0.051	
Median Time to tumour progression (months) (95 % CI)	5.7 (4.9 - 6.5)	3.9 (2.8 - 4.4)	6.1 (5.3 - 7.0)	3.9 (2.8 - 4.5)
Log Rank p-value*	0.001		0.008	
Time to Treatment Failure (months) (95 % CI)	4.5 (3.9 - 4.9)	2.7 (2.1 - 2.9)	4.7 (4.3 - 5.6)	2.7 (2.2 - 3.1)
Log Rank p-value*	0.001		0.001	
Overall response rate** (95 % CI)	41.3 % (34.8 - 48.1)	16.7 % (12.0 - 22.2)	45.5 % (37.8 - 53.4)	19.6 % (13.8 - 26.6)
Fisher's exact p-value*	< 0.001		< 0.001	

Abbreviation: CI = confidence interval

* p-value refers to comparison between arms.

** In the ALIMTA/cisplatin arm, randomized and treated (N = 225) and fully supplemented (N = 167)

A statistically significant improvement of the clinically relevant symptoms (pain and dyspnoea) associated with malignant pleural mesothelioma in the ALIMTA/cisplatin arm (212 patients) versus the cisplatin arm alone (218 patients) was demonstrated using the Lung Cancer Symptom Scale. Statistically significant differences in pulmonary function tests were also observed. The separation between the treatment arms was achieved by improvement in lung function in the ALIMTA/cisplatin arm and deterioration of lung function over time in the control arm.

There are limited data in patients with malignant pleural mesothelioma treated with ALIMTA alone. ALIMTA at a dose of 500 mg/m^2 was studied as a single-agent in 64 chemonaive patients with malignant pleural mesothelioma. The overall response rate was 14.1 %.

A multicentre, randomised, open label phase 3 study of ALIMTA versus docetaxel in patients with locally advanced or metastatic NSCLC after prior chemotherapy has shown median survival times of 8.3 months for patients treated with ALIMTA (Intent To Treat population n = 283) and 7.9 months for patients treated with docetaxel (ITT n = 288).

Efficacy of ALIMTA vs docetaxel in NSCLC - ITT Population

	ALIMTA	**Docetaxel**
Survival Time (months)	(n = 283)	(n = 288)
▪ Median (m)	8.3	7.9
▪ 95 % CI for median	(7.0 - 9.4)	(6.3 - 9.2)
▪ HR	0.99	
▪ 95 % CI for HR	(.82 - 1.20)	
▪ Non-inferiority p-value (HR)	.226	
Progression free survival (months)	(n = 283)	(n = 288)
▪ Median	2.9	2.9
▪ HR (95 % CI)	0.97 (.82 – 1.16)	
Time to treatment failure (TTTF – months)	(n = 283)	(n = 288)
▪ Median	2.3	2.1
▪ HR (95 % CI)	0.84 (.71 - .997)	
Response (n: qualified for response)	(n = 264)	(n = 274)
▪ Response rate (%) (95 % CI)	9.1 (5.9 - 13.2)	8.8 (5.7 - 12.8)
▪ Stable disease (%)	45.8	46.4

Abbreviations: CI = confidence interval; HR = hazard ratio; ITT = intent to treat; n = total population size.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of pemetrexed following single-agent administration have been evaluated in 426 cancer patients with a variety of solid tumours at doses ranging from 0.2 to 838 mg/m^2 infused over a 10-minute period. Pemetrexed has a steady-state volume of distribution of 9 l/m^2. *In vitro* studies indicate that pemetrexed is approximately 81 % bound to plasma proteins. Binding was not notably affected by varying degrees of renal impairment. Pemetrexed undergoes limited hepatic metabolism. Pemetrexed is primarily eliminated in the urine, with 70 % to 90 % of the administered dose being recovered unchanged in urine within the first 24 hours following administration. Pemetrexed total systemic clearance is 91.8 ml/min and the elimination half-life from plasma is 3.5 hours in patients with normal renal function (creatinine clearance of 90 ml/min). Between patient variability in clearance is moderate at 19.3 %. Pemetrexed total systemic exposure (AUC) and maximum plasma concentration increase proportionally with dose. The pharmacokinetics of pemetrexed are consistent over multiple treatment cycles.

The pharmacokinetic properties of pemetrexed are not influenced by concurrently administered cisplatin. Oral folic acid and intramuscular vitamin B_{12} supplementation do not affect the pharmacokinetics of pemetrexed.

5.3 Preclinical safety data

Administration of pemetrexed to pregnant mice resulted in decreased foetal viability, decreased foetal weight, incomplete ossification of some skeletal structures and cleft palate.

Administration of pemetrexed to male mice resulted in reproductive toxicity characterised by reduced fertility rates and testicular atrophy. This suggests that pemetrexed may impair male fertility. Female fertility was not investigated.

Pemetrexed was not mutagenic in either the *in vitro* chromosome aberration test in Chinese hamster ovary cells, or the Ames test. Pemetrexed has been shown to be clastogenic in the *in vivo* micronucleus test in the mouse.

Studies to assess the carcinogenic potential of pemetrexed have not been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol.
Hydrochloric acid.
Sodium hydroxide.

6.2 Incompatibilities

Pemetrexed is physically incompatible with diluents containing calcium, including lactated Ringer's Injection and Ringer's Injection. In the absence of compatibility studies (with other drugs and diluents), this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Unopened vial: This medicinal product does not require any special storage conditions.

Reconstituted and Infusion Solutions: When prepared as directed, reconstitution and infusion solutions of ALIMTA contain no antimicrobial preservatives. Chemical and physical in-use stability of reconstituted and infusion solutions of pemetrexed were demonstrated for 24 hours at refrigerated temperature or 25°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution / dilution has taken place in controlled and validated aseptic conditions.

6.5 Nature and contents of container

Powder in Type I glass vial. Rubber stopper.
Pack of 1 vial.

6.6 Instructions for use, handling and disposal

1. Use aseptic technique during the reconstitution and further dilution of pemetrexed for intravenous infusion administration.

2. Calculate the dose and the number of ALIMTA vials needed. Each vial contains an excess of pemetrexed to facilitate delivery of label amount.

3. Reconstitute 500-mg vials with 20 ml of sodium chloride 9 mg/ml (0.9 %) solution for injection, without preservative, resulting in a solution containing 25 mg/ml pemetrexed. Gently swirl each vial until the powder is completely dissolved. The resulting solution is clear and ranges in colour from colourless to yellow or green-yellow without adversely affecting product quality. The pH of the reconstituted solution is between 6.6 and 7.8. **Further dilution is required**.

4. The appropriate volume of reconstituted pemetrexed solution should be further diluted to 100 ml with sodium chloride 9 mg/ml (0.9 %) solution for injection, without preservative, and administered as an intravenous infusion over 10 minutes.

5. Pemetrexed infusion solutions prepared as directed above are compatible with polyvinyl chloride and polyolefin lined administration sets and infusion bags.

6. Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration. If particulate matter is observed, do not administer.

7. Pemetrexed solutions are for single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

Preparation and administration precautions: As with other potentially toxic anticancer agents, care should be exercised in the handling and preparation of pemetrexed infusion solutions. The use of gloves is recommended. If a pemetrexed solution contacts the skin, wash the skin immediately and thoroughly with soap and water. If pemetrexed solutions contact the mucous membranes, flush thoroughly with water. Pemetrexed is not a vesicant. There is not a specific antidote for extravasation of pemetrexed. There have been few reported cases of pemetrexed extravasation, which were not assessed as serious by the investigator. Extravasation should be managed by local standard practice as with other non-vesicants.

7. MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V., Grootslag 1-5, NL-3991 RA, Houten, The Netherlands.

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/290/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Lilly France S.A.S.
2 rue du Colonel Lilly
67640 Fegersheim
France

B CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, 4.2)

- **OTHER CONDITIONS**

The holder of this marketing authorisation must inform the European Commission about the marketing plans for the medicinal product authorised by this decision.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

ALIMTA 500 mg powder for concentrate for solution for infusion
pemetrexed

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 500 mg of pemetrexed (as pemetrexed disodium).

After reconstitution with 20 ml of sodium chloride 9 mg/ml (0.9 %) solution for injection, each vial contains 25 mg/ml of pemetrexed.
Further dilution required prior to intravenous infusion (see package leaflet).

3. LIST OF EXCIPIENTS

Mannitol, hydrochloric acid, sodium hydroxide.

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial, powder for concentrate for solution for infusion.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use after reconstitution and dilution.
Read the package leaflet before use.
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard unused contents appropriately.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V., Grootslag 1-5, NL-3991 RA, Houten, The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/290/001

13. MANUFACTURER'S BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

ALIMTA 500 mg powder for concentrate for solution for infusion
pemetrexed

2. METHOD OF ADMINISTRATION

For intravenous use after reconstitution and dilution.

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

Lot {number}

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

500 mg

B. PACKAGE LEAFLET

PACKAGE LEAFLET

Read all of this leaflet carefully before you start receiving ALIMTA.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

ALIMTA 500 mg powder for concentrate for solution for infusion
pemetrexed

Each vial contains 500 milligrams of pemetrexed (as pemetrexed disodium). After reconstitution, the solution contains 25 mg/ml of pemetrexed. Further dilution by healthcare provider is required prior to administration.
The other ingredients are mannitol, hydrochloric acid and sodium hydroxide.

Marketing Authorisation Holder:
Eli Lilly Nederland B.V., Grootslag 1-5, NL-3991 RA, Houten, The Netherlands

Manufacturer:
Lilly France S.A.S., rue du Colonel Lilly, 67640, Fegersheim, France

1. WHAT ALIMTA IS AND WHAT IT IS USED FOR

ALIMTA is a medicinal product used in the treatment of cancer.

ALIMTA is a powder for concentrate for solution for infusion in a vial. Each vial contains 500 mg of pemetrexed. Each pack of ALIMTA consists of one ALIMTA vial.

ALIMTA is a treatment for malignant pleural mesothelioma, which is given in combination with cisplatin, another anti-cancer medicine to patients who have not received prior chemotherapy.
ALIMTA is also a treatment for the advanced stage of lung cancer (of a certain type called non-small cell type) after other chemotherapy has been used.

2. BEFORE YOU ARE GIVEN ALIMTA

You should not be given ALIMTA if:
- you experienced in the past a severe allergic reaction to ALIMTA or any of the other ingredients of ALIMTA.
- Also if you are breast-feeding, you must discontinue breast-feeding during treatment with ALIMTA.
- you have recently received or are about to receive a vaccine against yellow fever.

Take special care with ALIMTA in the following cases:
If you have or have had problems with your kidney, talk to your doctor or hospital pharmacist as you may not be able to receive ALIMTA.

Before each infusion you will have samples of your blood taken to evaluate if you have sufficient kidney and liver function and to check that you have enough blood cells to receive ALIMTA. Your doctor may decide to change the dose or put off treating you depending on your general condition and if your blood cell counts are too low. If you are also receiving cisplatin, your doctor will make sure that you are properly hydrated and receive appropriate treatment before and after receiving cisplatin to prevent vomiting.

If you have been recently vaccinated, please tell your doctor.

If you have an accumulation of fluid around your lung, your doctor may decide to remove the fluid before giving you ALIMTA.

If you would like to father a child during the treatment or in the 6 months following receipt of treatment, seek advice from your doctor or pharmacist. You may want to seek counselling on sperm storage before starting your therapy.

Pregnancy
If you are pregnant, thinking about becoming pregnant or think you may be, **tell your doctor**. The use of ALIMTA should be avoided during pregnancy. Your doctor will discuss with you the potential risk of taking ALIMTA during pregnancy. Women must use effective contraception during treatment with ALIMTA.

Breast-feeding
If you are breast-feeding, tell your doctor.
Breast-feeding must be discontinued during ALIMTA treatment.

Driving and using machines
ALIMTA may make you feel tired. Be careful when driving a car or operating machine(s).

Taking other medicines
Please tell your doctor if you are taking any medicine for pain or inflammation (swelling), such as medicines called “nonsteroidal anti-inflammatory drugs” (NSAIDs), including medicines purchased without a doctor’s prescription (such as ibuprofen). There are many sorts of NSAIDs with different durations of activity. Based on the planned date of your infusion of ALIMTA and/or on the status of your kidney function, your doctor needs to advise you on which medicines you can take and when you can take them. If you are unsure, ask your doctor or pharmacist if any of your medicines are NSAIDs.

Please inform your doctor or hospital pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

3. HOW ALIMTA IS GIVEN

The dose of ALIMTA is 500 milligrams for every square metre of your body’s surface area. Your height and weight are measured to work out the surface area of your body. Your doctor will use this body surface area to work out the right dose for you. This dosage may be adjusted, or treatment may be delayed depending on your blood cell counts and on your general condition. A hospital pharmacist, nurse or doctor will have mixed the ALIMTA powder with sodium chloride 9 mg/ml (0.9 %) solution for injection before it is given to you.

You will always receive ALIMTA by infusion into one of your veins. The infusion will last approximately 10 minutes.

When using ALIMTA in combination with cisplatin:
The doctor or hospital pharmacist will work out the dose you need based on your height and weight. Cisplatin is also given by infusion into one of your veins, and is given approximately 30 minutes after the infusion of ALIMTA has finished. The infusion of cisplatin will last approximately 2 hours.

You should usually receive your infusion once every 3 weeks.

Additional medicines:
Corticosteriods: your doctor will prescribe you steroid tablets (equivalent to 4 milligram of dexamethasone twice a day) that you will need to take on the day before, on the day of, and the day after ALIMTA treatment. This medicine is given to you to reduce the frequency and severity of skin reactions that you may experience during your anticancer treatment.

Vitamin supplementation: your doctor will prescribe you oral folic acid (vitamin) or a multivitamin containing folic acid (350 to 1000 micrograms) that you must take once a day while you are taking ALIMTA. You must take at least 5 doses during the seven days before the first dose of ALIMTA. You must continue taking the folic acid for 21 days after the last dose of ALIMTA. You will also receive an injection of vitamin B_{12} (1000 micrograms) in the week before administration of ALIMTA and then approximately every 9 weeks (corresponding to 3 courses of ALIMTA treatment). Vitamin B_{12} and folic acid are given to you to reduce the possible toxic effects of the anticancer treatment.

4. POSSIBLE SIDE EFFECTS

Like all medicines, ALIMTA can have side effects.

You must contact your doctor immediately if you notice any of the following:
- Fever or infection: if you have a temperature of 38ºC or greater, sweating or other signs of infection (since you might have less white blood cells than normal).
- If you start feeling chest pain or having a fast heart rate.
- If you have pain, redness, swelling or sores in your mouth.
- Allergic reaction: if you develop skin rash / burning or prickling sensation, or fever.
- If you experience tiredness, feeling faint, becoming easily breathless or if you look pale (since you might have less haemoglobin than normal).
- If you experience bleeding from the gums, nose or mouth or any bleeding that would not stop, reddish or pinkish urine, unexpected bruising (since you might have less platelets than normal).

Other side effects may include:
General: fatigue (tiredness), dehydration.
Gastrointestinal tract: pain in the abdomen, upset stomach, constipation, nausea, vomiting, loss of appetite, diarrhoea.
Nervous system: taste change, loss of sensation, muscle weakness.
Skin: irritation of the skin and itching, hair loss, burning or prickling sensation.
Eye disorders: conjunctivitis (inflamed eye).
Liver and kidney: abnormal blood tests, kidney failure.

You might have any of these symptoms and/or conditions. You must tell your doctor as soon as possible when you start experiencing any of these side effects.

Uncommonly some patients have experienced a stroke or “mini-stroke” while receiving ALIMTA usually in combination with another anticancer therapy.

If you are concerned about any side effect(s), talk to your doctor.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING ALIMTA

Keep out of the reach and sight of children.
This medicinal product does not require any special storage conditions.

Do not use after the expiry date shown on the pack.

Reconstituted and Infusion Solutions: The product should be used immediately. When prepared as directed**,** chemical and physical in-use stability of reconstituted and infusion solutions of pemetrexed were demonstrated for 24 hours at refrigerated temperature or 25°C.

This medicinal product is for single use only, any unused solution should be discarded under the local requirements.

6. FURTHER INFORMATION

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last approved on {date}

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The following information is intended for medical or healthcare professionals only:

Instructions for use, handling and disposal.

1. Use aseptic technique during the reconstitution and further dilution of pemetrexed for intravenous infusion administration.

2. Calculate the dose and the number of ALIMTA vials needed. Each vial contains an excess of pemetrexed to facilitate delivery of label amount.

3. Reconstitute 500-mg vials with 20 ml of sodium chloride 9 mg/ml (0.9 %) solution for injection, without preservative, resulting in a solution containing 25 mg/ml pemetrexed. Gently swirl each vial until the powder is completely dissolved. The resulting solution is clear and ranges in colour from colourless to yellow or green-yellow without adversely affecting product quality. The pH of the reconstituted solution is between 6.6 and 7.8. **Further dilution is required**.

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5. Pemetrexed infusion solutions prepared as directed above are compatible with polyvinyl chloride and polyolefin lined administration sets and infusion bags.

6. Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration. If particulate matter is observed, do not administer.

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